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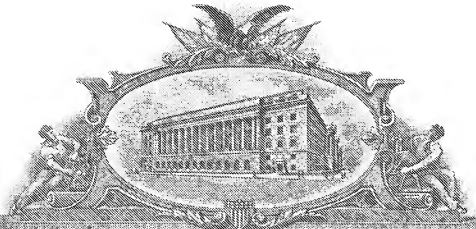

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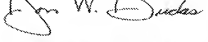

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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

PROCESS FOR ISOLATION OF ERGOT ALKALOIDS FROM ERGOT

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 12

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Respectfully submitted,

SIGNATURE Dennis A. Emma

Date February 20, 2004

REGISTRATION NO. 50980 *(if appropriate)*

TYPED or PRINTED NAME Dennis A. Emma, Ph.D.

Docket Number: GAL0019-P-USA

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Docket Number	GAL0020-P-USA

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Ladislav Cvak, Jiri Holan, and Lubomir Roder
Serial Number:	To be assigned
Filing Date:	HEREWITH
Title:	PROCESS FOR ISOLATION OF ERGOT ALKALOIDS FROM ERGOT
Attorney Docket No.:	GAL0020-P-USA

CERTIFICATION UNDER 37 C.F.R. § 1.10

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Dear Sir:

Enclosed herewith for filing with the United States Patent and Trademark Office in the above-identified Provisional Patent Application pursuant to 37 C.F.R. § 1.53 (c) are the following documents:

1. Provisional Application Cover Sheet (one page);
2. Provisional Patent Application (12 pages); and
3. Return Postcard.

Respectfully Submitted,

Dennis A. Emma

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PROCESS FOR ISOLATION OF ERGOT ALKALOIDS FROM ERGOT

Inventors: Ladislav Cvak, Jiri Holan, Lubomir Roder
(Attorney Docket Number GAL0020-P-USA)

FIELD OF THE INVENTION

[0001] The present invention relates to a process for extraction and purification of ergot alkaloids and in particular to the extraction and purification of ergot peptide alkaloids from the fungi *Claviceps purpurea*.

BACKGROUND OF THE INVENTION

[0002] Ergot peptide alkaloids, also called ergopeptines, are natural products used for the manufacture of drugs. They are known to have therapeutic value themselves (e.g., ergotamine) or in their hydrogenated form such as their dihydroderivatives, e.g., dihydroergotamine, dihydroergocristine, etc. Additionally, they are known starting compounds for the partial synthesis of some semisynthetic drugs, such as nicergoline, pergolide, etc.

[0003] Ergot alkaloids of the peptide type are produced by the fungi *Claviceps purpurea* which can be cultivated under parasitic conditions (growing on fields using rye as the host plant) or saprophytic conditions (i.e. fermentation). Although the processes used for isolating ergopeptines from field ergot and from fermentation broth share common features (i.e. similar solvents and purification techniques), they differ substantially in the nature of the starting material.

[0004] Several processes for extraction of ergot have been described in the patent literature. The disclosed processes typically reflect the state of the art at the time and in country of their origin. Individual processes, mainly that used for large-scale isolation of ergot alkaloids differ in the solvents that were used. For example, the known older processes used aqueous ethanol or methanol (DP 47 315, DP 697 760), newer processes used chlorinated hydrocarbons (DE 2 113 281, DE 2 637 764, DD 10 059), diethylether (CS 264 880, CS 264 881), acetone (DE 1 695 986), methyl isobutylketone (BE 891 421) or ethylacetate (DE 2 949 593, EP 22 418). Some of these solvents, however, are not currently acceptable for large scale process due to safety and ecological concerns (diethylether and chlorinated hydrocarbons being examples). Some of the known solvents are additionally not selective enough to produce ergot alkaloids

with required purity to be practical for manufacturing, e.g., aqueous methanol, aqueous ethanol and acetone.

[0005] Moreover, ergot contains up to 30% of oil and other lipids. Prior art processes used solvents that extracted other components of ergot, mainly oil and necessarily required an operation for the separation of alkaloids from the associated lipids. However, not all the known solvents are suitable for direct elimination of lipids by liquid-liquid extraction and therefore the isolation procedures including concentration of the primary extracts by evaporation and dissolving the residue in another solvent, added to the complexity of the process. Additionally, the evaporation of the primary extract containing oil and other ballast components is harmful to the extracted alkaloids.

[0006] Natural ergopeptines as derivatives of lysergic acid readily isomerize to derivatives of isolysergic acid, the so-called ergopeptinines. This fact usually complicates the isolation of ergopeptines because the primary extracts obtained from ergot always contain mixtures of ergopeptines and ergopeptinines, which makes it difficult to obtain crystalline product, thus precluding crystallization techniques, which is an otherwise efficient means of purification.

[0007] Therefore, processes for large-scale isolation of ergot alkaloids, using safe and environmentally friendly solvents with simple and efficient purification operations are still desirable.

SUMMARY OF THE DISCLOSURE

[0008] The present invention represents a facile method of extracting ergot alkaloids from ergot and purifying of the primary extract providing the ergot alkaloids in high yields and quality.

[0009] These and other advantages are satisfied by a process of isolating an ergot alkaloid from ergot, which includes extracting the ergot with a mixture comprising toluene and ethanol. By using the extraction mixture, ergot alkaloids can be transferred to a primary extract in high yield. The inventive process makes use of relatively benign solvents to extract ergot in any form, including cut, milled or pressed ergot.

[0010] In further embodiments of the present invention, the primary extract is subjected to liquid-liquid extractions to separate the ergot alkaloid from the lipids present in the primary extract. The purification enables to obtain the ergot alkaloids as a crystalline product in high yield and quality.

[0011] The present invention advantageously provides a facile method of extracting ergot and obtaining the ergot alkaloids in a relatively simple process that can be scaled-up to industrial processes.

[0012] Additional advantages of the present invention will become readily apparent to those skilled in this art from the following detailed description, wherein only the preferred embodiment of the invention is shown and described, simply by way of illustration of the best mode contemplated of carrying out the invention. As will be realized, the invention is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the invention. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0013] The present invention is directed to the isolation of ergot alkaloids from ergot, i.e., *Claviceps purpurea*, by a simple, effective extraction process employing relatively safe and environmentally acceptable solvents. In practicing one aspect of the present invention, ergot is extracted with a toluene/ethanol mixture to form a primary extract which is further subjected to liquid-liquid extractions to further isolate and purify the ergot alkaloids obtained in the primary extract.

[0014] After experimentation and investigation, it was discovered that an extraction mixture containing at least about 5 % (v/v) ethanol in toluene is beneficial in extracting ergot. When the concentration of ethanol is lower, the extraction of ergot alkaloids from ergot is not very efficient. The determination of the higher limit of the ethanol content is based on the intended selectivity of the extraction. For example, the more ethanol the more polar ballast components are extracted and the more difficult it is to further process the primary extract. In one embodiment of the present invention, the concentration of ethanol in the extraction solvent is preferably not in excess of about 30 % (v/v). The process does not limit the temperature of the extraction because the usually unwanted isomerization of ergopeptines, which can occur at high temperature, does not impede the crystallization of the product. Therefore the higher temperature, the more efficient is the extraction. Nevertheless, temperature higher than about 50 °C is not economical. In a preferred embodiment, ergot is

extracted with a toluene/ethanol mixture within a temperature range of between about 20 °C to about 50 °C.

[0015] In practicing an embodiment of the present invention, the primary extract is further subjected to liquid–liquid extraction using an aqueous solution containing an acid, e.g., hydrochloric acid. The additional step of liquid-liquid extracting the primary extract advantageously permits the facile separation of the generally more polar and hydrophilic alkaloids from the less polar and hydrophobic oils and lipids. Hence, liquid-liquid extraction of the primary extract with an aqueous solution containing an acid results in transferring the ergot alkaloids into the aqueous solution while leaving any oil in the primary extract. This aqueous extract containing alkaloids can then be easily separated from the primary extract and further aids in the isolation and purification of the alkaloids. Any acid can be used with the aqueous solution. However, it was determined based on experimentation that hydrochloric acid was preferable due to the high solubility of ergopeptines hydrochlorides in aqueous hydrochloric acid solutions.

[0016] In another aspect of practicing the present invention, an alcohol can be added to the aqueous solution to prevent or reduce the formation of an emulsion therein. It was discovered that under certain conditions, the aqueous solution can form an emulsion, which would reduce its ability to isolate the alkaloids. Hence, an emulsion inhibiting amount of alcohol, or similarly functioning solvent, can be added to the aqueous solution for optimum results. For example, ethanol can be added to an aqueous solution containing hydrochloric acid used for extraction of alkaloids from the primary extract. The concentration of acid in the aqueous solution is not critical but the solution should contain at least one equivalent of acid to extract the alkaloids from the primary extract quantitatively. For example, the aqueous solution of hydrochloric acid can comprise from about 30 % to 60 % (v/v) of water, about 70 to 40 % (v/v) of ethanol and about 0.05 to 1.0 % (w/w) of hydrogen chloride.

[0017] The obtained aqueous extract is then made alkaline, thereby facilitate the alkaloid's transfer into organic solvent by another step of liquid-liquid extraction. In one embodiment of the present invention, the aqueous extract is made alkaline by increase its pH to above 7.0. This can be done with any aqueous alkaline solution as, for example, with an aqueous solution of sodium hydroxide. Upon increasing the alkalinity of the aqueous extract, the aqueous extract is subjected liquid-liquid extraction with toluene. Using other solvent than toluene is possible but it is lacking the technical sense. The toluene extract resulting from this

liquid-liquid extraction step contains practically only ergot alkaloids and therefore it is denominated as the purified toluene extract.

[0018] It was discovered that the partial evaporation of the purified toluene extract resulted in crystalline product. In another aspect of the present invention, the final isolation of alkaloids from the purified toluene extract is accomplished by simple evaporation of the solvent and crystallization of the obtained residue from toluene. It was found that some alkaloids, namely ergotamine and ergocristine can be obtained as crystalline products by merely evaporating the toluene extract. The fact that the organic solvent may contain a mixture of ergopeptine and ergopeptinine has not adversely influenced the crystallization of these products, because a crystalline mixture of corresponding ergopeptine and ergopeptinine *e.g.*, the mixture of ergotamine and ergotaminine or the mixture of ergocristine and ergocristinine, is obtained. Without being bound to any theory, it appears that the extraction and purification techniques of the present invention result in the isolation of ergot alkaloids in substantially pure form and without crystallization inhibiting impurities. Thus, even when there is a mixture of alkaloids extracted, a crystalline product can be obtained after partial evaporation of the solvent. Moreover, potential transformations of the ergot alkaloids such as isomerization of ergot alkaloids, which can occur at high temperature, does not appear to influence the isolation and crystallization of the products obtained after evaporation of the solvent. Hence, extraction at high temperatures does not adversely effect the present process. The crystallization of alkaloids from toluene has surprisingly high purification effect as it is demonstrated in Examples 1 and 2 by comparison of the alkaloid composition of the first and the second crops.

[0019] Under certain circumstances, however, it was found that the toluene extract can contain a mixture of alkaloids *e.g.*, a mixture of ergotoxine alkaloids, which limit their ability to crystallize. The alkaloid composition of the toluene extract corresponds to the spectrum of alkaloids produced by the used strain of ergot. When such a mixture of ergotoxine alkaloids is present in the toluene extract, little or no crystalline product can be obtained directly from toluene. However, crystallization can be accomplished by addition of one or more aliphatic hydrocarbon, *e.g.*, a C_5-C_8 hydrocarbon such as hexane or heptane, to the solution. Such crystallization technique has no effect on the alkaloid composition, but it can still produce a crystalline product free of ballast components and suitable for further use as it is demonstrated in Example 3.

EXAMPLES

[0020] The following examples illustrate but do not limit the process. The examples illustrate a process of isolating several ergot alkaloids from a variety of ergot in greater than 90% purity.

Example 1

[0021] About 20,000 kg of ergot (ergocristine strain GAL 130) was extracted under counter current conditions by a mixture of toluene and ethanol 87:13 (v/v) on a continual extractor of a carrousel type. Approximately 64 m^3 of primary extract was obtained. The primary extract was then extracted on a continual extractor Westfalia by a mixture of ethanol and water 1:1 (v/v), containing 0.2% (w/w) hydrogen chloride. Approximately 28 m^3 of aqueous extract resulted. The aqueous extract was made alkaline to about pH 7.3 by a 5% (w/w) aqueous sodium hydroxide solution and extracted with toluene on a continual extractor Westfalia. About 16 m^3 of toluene extract was received. The toluene extract was evaporated to about 1000 kg and the resulting crystalline product was filtered off, washed with toluene and dried for 3 hours in a vacuum dryer at 60°C and 50 mbar, to obtain 152 kg of a First crop of Crude ergocristine. The mother liquors were evaporated to about 400 kg and 1500 L of technical hexane was added. The precipitated crystalline product was filtered off, washed with technical hexane and dried, to obtain 89 kg of a Second crop of Crude ergocristine.

[0022] Analytical results:

	First crop	Second crop
Assay by titration	93.1 %	92.6 %
Ergocristine	30.9 %	20.0 %
Ergocristinine	59.3 %	36.6 %
α-ergokryptine	2.4 %	10.5 %
α-ergokryptinine	3.9 %	17.2 %
Sum of other alkaloids	2.6 %	15.7 %

Example 2

[0023] About 20, 000 kg of ergot (ergotamine strain GAL 404) was extracted counter current way by a mixture of toluene and ethanol 84:16 (v/v) on a continual extractor of a carrousel type and 78 m^3 of primary extract was obtained. The primary extract was extracted on a continual extractor Westfalia by a mixture of ethanol and water 6:4 (v/v), containing 0.2% (w/w) hydrogen chloride and 18 m^3 of aqueous extract resulted. The aqueous extract was made alkaline by increasing its pH to pH 7.3 by 5% (w/w) aqueous sodium hydroxide and extracted by toluene on continual extractor Westfalia. 30 m^3 of toluene extract was received. The toluene extract was evaporated to about 1000 kg and the resulting crystalline product was filtered off, washed with toluene and dried for 3 hours in vacuum dryer at 60°C and 50 mbar, resulting in about 181 kg of a First crop of Crude ergotamine. The mother liquors were evaporated to about 100 kg and the crystalline product was filtered off, washed with toluene and dried, obtaining 19 kg of Second crop of Crude ergotamine.

[0024] Analytical results:

	First crop	Second crop
Assay by titration	95.0 %	90.6 %
Ergotamine	24.7 %	31.5 %
Ergotaminine	71.7 %	51.5 %
Sum of other alkaloids	3.6 %	17.0 %

Example 3

[0025] About 20, 000 kg of ergot (ergotoxine strain GAL 310) was extracted counter current way by a mixture of toluene and ethanol 87:13 (v/v) on a continual extractor of a carrousel type. Approximately 69 m^3 of primary extract was obtained. The primary extract was extracted on a continual extractor Westfalia by a mixture of ethanol and water 1:1 (v/v), containing 0.2% (w/w) hydrogen chloride resulting in 27 m^3 of aqueous extract. The aqueous extract was made alkaline by increasing the pH of the aqueous extract to about pH 7.3 by 5% (w/w) aqueous sodium hydroxide. It was then extracted with toluene on continual extractor Westfalia resulting in about 17 m^3 of toluene extract was received. The toluene extract was evaporated to about 800 kg and 1800 L of technical hexane was added. The precipitated

crystalline product was filtered off, washed with technical hexane and dried for 3 hours in vacuum dryer at 60°C and 50 mbar obtaining 151 kg of Crude ergotoxine.

[0026] Analytical results:

Assay by titration	94.4 %
Ergocornine	18.1 %
Ergocorninine	29.2 %
α-ergokryptine	11.7 %
α-ergokryptinine	18.5 %
β-ergokryptine	6.3 %
β-ergokryptinine	11.6 %
Sum of other alkaloids	4.6 %

[0027]

[0028] In this disclosure there is described only the preferred embodiments of the invention and but a few examples of its versatility. It is to be understood that the invention is capable of use in various other combinations and environments and is capable of changes or modifications within the scope of the inventive concept as expressed herein.

WHAT IS CLAIMED IS:

1. A process for isolating ergot alkaloids from ergot, the process comprising:

extracting ergot with a mixture of toluene and ethanol to obtain a primary extract;

extracting the primary extract with an aqueous solution of hydrochloric acid to obtain an aqueous extract;

increasing the pH of the aqueous extract to above 7.0;

extracting the aqueous extract having a pH above 7.0 with toluene to obtain a purified toluene extract;

partial evaporating the purified toluene extract to obtain crystalline ergot alkaloids; and

separating the crystalline ergot alkaloids by filtration.

2. The process according to claim 1, wherein the mixture of toluene and ethanol contains about 5 % to about 30 % (v/v) of ethanol.

3. The process according to claim 1, wherein the extraction of ergot is performed in a counter current way on a battery of percolators or on a continuous extractor.

4. The process according to claim 1, wherein the extraction of ergot is performed at the temperature in the range of about 20 °C to about 50 °C.

5. The process according to claim 1, wherein the aqueous solution of hydrochloric acid contains from about 30 % to 60 % (v/v) of water, about 70 % to 40 % (v/v) of ethanol and about 0.05 % to 1.0 % (w/w) of hydrogen chloride.

6. The process according to claim 1, wherein the crystalline ergot alkaloid obtained by the partial evaporation of the purified toluene extract is predominantly a mixture of ergocristine and ergocristinine.

7. The process according to claim 1, wherein the crystalline ergot alkaloid obtained by the partial evaporation of the purified toluene extract is predominantly a mixture of ergotamine and ergotaminine.

8. A process of isolating an ergot alkaloid from ergot, the process comprising extracting ergot with a mixture comprising toluene and about 5 % to about 30 % (v/v) of ethanol to form a primary extract to isolate an ergot alkaloid from ergot.

9. The process of claim 8 further comprising extracting the primary extract with an aqueous solution containing an acid to transfer the ergot alkaloid from the primary extract to the aqueous extract.

10. The process according to claim 9 comprising extracting the primary extract with an aqueous hydrochloric acid solution.

11. The process according to claim 10, further comprising increasing the pH of the aqueous extract to above 7.0.

12. The process according to claim 11, further comprising extracting the aqueous extract having a pH above 7.0 with toluene to transfer the ergot alkaloid from the aqueous solution to the toluene and obtaining the purified toluene extract.

13. The process of claim 12 further comprising partial evaporating of the solvent from the purified toluene extract and recovering crystalline ergot alkaloid by crystallization from toluene.

14. The process according to claim 13, further comprising adding one or more $C_5 - C_8$ aliphatic hydrocarbons to the concentrate after partial evaporation of toluene and obtaining the crystalline ergot alkaloid.

15. The process according to claim 14, wherein the one or more aliphatic $C_5 - C_8$ hydrocarbons is hexane or heptane.

16. The process of claim 15, comprising isolating the crystalline ergot alkaloid in greater than 90% purity.

17. The process of claim 8 further comprising extracting the primary extract with an aqueous solution containing an acid to transfer the ergot alkaloid to the aqueous solution, increasing the pH of the aqueous solution to above 7, extracting the ergot alkaloid from the aqueous solution to toluene, partial evaporating the purified toluene extract and separating the crystalline ergot alkaloid from toluene or a mixture of toluene and one or more aliphatic $C_5 - C_8$ hydrocarbon by filtration.

18. A process of isolating crystalline ergot alkaloid, the process comprising:

extracting ergot with a mixture comprising toluene and ethanol to form a primary extract containing ergot alkaloids;

transferring the ergot alkaloids from the primary extract to an aqueous solution containing an acid by liquid-liquid extraction;

increasing the pH of the aqueous solution to above 7.0;

transferring the ergot alkaloid from the aqueous solution having a pH above 7.0 to toluene by liquid-liquid extraction to form a purified toluene extract;

partial evaporation of the purified toluene extract to facilitate the crystallization of ergot alkaloids, and

separating the crystalline ergot alkaloids by filtration.

ABSTRACT

Ergot alkaloids are isolated from ergot in high yields and purity by a process including extracting *Claviceps purpurea*, i.e. ergot, with a toluene/ethanol solvent mixture to obtain a primary extract. The primary extract is further subjected to two steps of liquid-liquid extraction to purify the alkaloids resulting in a purified toluene extract. The toluene extract is further partially evaporated and the crystalline product is obtained by crystallization from toluene or a mixture of toluene and an aliphatic hydrocarbon. The final isolation of the crystalline product is accomplished by filtration.